BIOACTIVE RENAL CELLS

RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 15/925,172, filed Mar. 19, 2018, which is continuation of U.S. patent application Ser. No. 13/697,206, which is a national stage application, filed under 35 U.S.C. § 371, of International Application No. PCT/US11/36347 filed May 12, 2011, which claims the benefit under 35 U.S.C. § 119 of U.S. Provisional Application No. 61/473,111, filed Apr. 7, 2011; U.S. Provisional Application No. 61/441,423, filed Feb. 10, 2011; U.S. Provisional Application No. 61/413,382, filed Nov. 12, 2010; U.S. Provisional Application No. 61/412,933, filed Nov. 12, 2010; U.S. Provisional Application No. 61/388,765, filed Oct. 1, 2010; U.S. Provisional Application No. 61/376,586, filed Aug. 24, 2010; U.S. Provisional Application No. 61/372,077, filed Aug. 9, 2010; U.S. Provisional Application No. 61/371,888, filed Aug. 9, 2010; U.S. Provisional Application No. 61/353,895, filed Jun. 11, 2010; and U.S. Provisional Application No. 61/334,032, filed May 12, 2010, the entire contents of each of which are hereby incorporated by reference herein.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII text format and is hereby incorporated by reference in its entirety. Said ASCII text copy, created on Mar. 19, 2018, is named "050400_506C01US_Sequence_Listing.txt" and is 1,154 bytes in size.

FIELD OF THE INVENTION

[0003] The present invention relates to bioactive renal cell populations or fractions that lack cellular components as compared to a healthy individual yet retain therapeutic properties, and methods of isolating and culturing the same, as well as methods of treating a subject in need with the cell populations. In addition, the present invention relates to methods of providing regenerative effects to a native kidney using bioactive renal cell populations.

BACKGROUND OF THE INVENTION

[0004] Chronic Kidney Disease (CKD) affects over 19 million people in the United States and is frequently a consequence of metabolic disorders involving obesity, diabetes, and hypertension. Examination of the data reveals that the rate of increase is due to the development of renal failure secondary to hypertension and non-insulin dependent diabetes mellitus (NIDDM) (United States Renal Data System: Costs of CKD and ESRD. ed. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2007 pp 223-238)—two diseases that are also on the rise worldwide. Obesity, hypertension, and poor glycemic control have all been shown to be independent risk factors for kidney damage, causing glomerular and tubular lesions and leading to proteinuria and other systemically-detectable alterations in renal filtration function (Aboushwareb, et al., World J Urol, 26: 295-300, 2008; Amann, K. et al., Nephrol Dial Transplant, 13: 1958-66, 1998). CKD patients in stages 1-3 of progression are managed by lifestyle changes and pharmacological interventions aimed at controlling the underlying disease state(s), while patients in stages 4-5 are managed by dialysis and a drug regimen that typically includes anti-hypertensive agents, erythropoiesis stimulating agents (ESAs), iron and vitamin D supplementation. Regenerative medicine technologies may provide next-generation therapeutic options for CKD. Presnell et al. WO/2010/056328 describe isolated renal cells, including tubular and erythropoietin (EPO)-producing kidney cell populations, and methods of isolating and culturing the same, as well as methods of treating a subject in need with the cell populations. There is a need for new treatment paradigms that provide substantial and durable augmentation of kidney functions, to slow progression and improve quality of life in this patient population.

SUMMARY OF THE INVENTION

[0005] In one aspect, the present invention provides a method for providing a regenerative effect to a native kidney. In one embodiment, the method includes the step of in vivo contacting the native kidney with products secreted by an enriched renal cell population. In another embodiment, the products are secreted by an enriched renal cell population that is not part of a construct, as described herein, e.g., the cell population is not seeded on a scaffold. In one other embodiment, the products are secreted from a renal cell construct comprising an enriched renal cell population directly seeded on or in a scaffold. In another embodiment, the secretion of the products is bioresponsive to oxygen levels. Secretion may be induced by a less than atmospheric oxygen level. In one other embodiment, the lower oxygen level is less than about 5% oxygen.

[0006] In one embodiment, the regenerative effect is a reduction in epithelial-mesenchymal transition (EMT). The reduction in EMT may be achieved via attenuation of TGF-β signalling and/or attenuation of Plasminogen Activator Inhibitor-1 (PAI-1) signalling. In another embodiment, the regenerative effect is a reduction in renal fibrosis and/or a reduction in renal inflammation. In some embodiments, the reduction in inflammation may be mediated by NFκB. In one other embodiment, the regenerative effect is characterized by differential expression of a stem cell marker in the native kidney. The expression may be an upregulation of marker expression in the in vivo contacted native kidney relative to expression in a non-contacted native kidney.

[0007] In one aspect, the enriched renal cell population includes one or more cell populations, i.e., an admixture, as described herein. In one embodiment, the population includes a first cell population, B2, that contains an enriched population of tubular cells. In another embodiment, the population includes an admixture of human renal cells having a first cell population, B2, and a second cell population, which contains one or more of erythropoietin (EPO)-producing cells, glomerular cells and vascular cells. In one other embodiment, the second cell population is a B4 cell population. In yet another embodiment, the second cell population is a B3 cell population.

[0008] In one embodiment, the admixture further includes a third cell population having one or more of erythropoietin (EPO)-producing cells, glomerular cells and vascular cells. In another embodiment, the third cell population is a B4 cell population. In one other embodiment, the third cell population is a B3 cell population.

[0009] In all embodiments, the B2 cell population has a density between about 1.045 g/mL and about 1.052 g/mL. In all embodiments, the B4 cell population has a density between about 1.063 g/mL and about 1.091 g/mL. In all